ACTIVIN A ANTIBODY FORMULATIONS AND METHODS OF USE THEREOF

RELATED APPLICATIONS

[0001] The instant application claims priority to U.S. Provisional Application No. 63/040,589, filed on Jun. 18, 2020, the entire contents of which are expressly incorporated herein by reference in their entireties.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Aug. 30, 2021, is named 118003-75702_SL.txt and is 9,972 bytes in size.

FIELD

[0003] The present invention relates to the field of therapeutic antibody formulations. More specifically, the present invention relates to the field of pharmaceutical formulations comprising an antibody that specifically binds to human Activin A.

BACKGROUND

[0004] Fibrodysplasia ossificans progressiva (FOP), also known as Munchmeyer disease, is an autosomal dominant disorder characterized by early onset, episodic and progressive ossification of skeletal muscle and associated connective tissue. In FOP subjects, bone forms in soft tissue outside of the normal skeleton, a process known as heterotopic ossification (HO), which can lead to the development of a secondary skeleton and progressively restricts the patient's ability to move. Removal of the new bone formation has been shown to be ineffective and leads to the development of additional new bone growth.

[0005] FOP is driven by mutations in the intracellular domain of ACVR1 (ALK2), with the great majority altering Arginine 206 to Histidine (R206H) (Pignolo, R. J. et al. 2011, *Orphanet J. Rare Dis.* 6:80). ACVR1 is a type I receptor for bone morphogenic proteins (BMPs). The R206H mutation, among others, is believed to increase the sensitivity of the receptor to activation and render it more resistant to silencing.

[0006] Although certain types of drugs have been used to relieve pain and swelling associated with FOP during flare-ups, no effective medical treatment is currently known for FOP. Antibodies to Activin A are one example of a therapeutically relevant macromolecule that requires proper formulation. Although some anti-Activin A antibodies are known, there nonetheless remains a need in the art for novel pharmaceutical formulations comprising anti-Activin A antibodies that are sufficiently stable and suitable for administration to patients.

SUMMARY

[0007] Methods to produce antibodies useful as human therapeutics include generation of chimeric antibodies and humanized antibodies (see, for example, U.S. Pat. No. 6,949,245). See, for example, WO 94/02602 (Abgenix) and U.S. Pat. No. 6,596,541 (Regeneron Pharmaceuticals), which publications are herein specifically incorporated by reference, describing methods of generating nonhuman transgenic mice capable of producing human antibodies. U.S. Pat. No. 9,718,881 discloses antibodies to human Activin A, and is incorporated in its entirety herein by reference.

[0008] Therapeutic antibodies must be formulated in a manner that not only makes the antibodies suitable for administration to patients, but also in a manner that maintains their stability during storage and subsequent use. For example, therapeutic antibodies in liquid solution are prone to fragmentation, precipitation, aggregation, and undesired chemical modifications unless the solution is formulated properly. The stability of an antibody in liquid formulation depends not only on the kinds of excipients used in the formulation, but also on the amounts and proportions of the excipients relative to one another. Furthermore, other considerations aside from stability must be taken into account when preparing a liquid antibody formulation. Examples of such additional considerations include the viscosity of the solution and the concentration of antibody that can be accommodated by a given formulation, and the visual quality or appeal of the formulation. Thus, when formulating a therapeutic antibody, great care must be taken to arrive at a formulation that remains stable, contains an adequate concentration of antibody, and possesses a suitable viscosity as well as other properties which enable the formulation to be conveniently administered to patients.

[0009] The present invention satisfies the aforementioned need by providing pharmaceutical formulations comprising a human antibody that specifically binds to human Activin A.

[0010] In one aspect, a liquid pharmaceutical formulation is provided, comprising: (i) an antibody that specifically binds to Activin A; (ii) a buffer; (iii) an organic cosolvent; and (iv) thermal stabilizers.

[0011] In another aspect, the present invention provides a pharmaceutical formulation comprising: (i) an anti-human Activin A antibody, or antigen-binding portion thereof; (ii) a buffer at pH of 6.3±0.3; (iii) an organic cosolvent; and (iv) one or more thermal stabilizers.

[0012] In some embodiments, the antibody, or the antigen-binding portion thereof, comprises the following six CDR sequences: (a) an HCDR1 having the sequence GGSFSSHF (SEQ ID NO.: 1); (b) an HCDR2 having the sequence ILYTGGT (SEQ ID NO.: 2); (c) an HCDR3 having the sequence ARARSGITFTGIIVPGSFDI (SEQ ID NO.: 3); (d) an LCDR1 having the sequence QSVSSSY (SEQ ID NO.: 4); (e) an LCDR2 having the sequence GAS (SEQ ID NO.: 5); and (f) an LCDR3 having the sequence QQYGSSPWT (SEQ ID NO.: 6).

[0013] In some embodiments, the antibody has a molecular weight of about 145,235.3 Da.

[0014] In some embodiments, the concentration of the antibody, or the antigen-binding portion thereof, is 60 mg/mL±6 mg/mL.

[0015] In some embodiments, the buffer is a histidine buffer. In some embodiments, the histidine concentration is 10 mM±2 mM .

[0016] In some embodiments, the organic cosolvent is polysorbate 20. In some embodiments, the polysorbate 20 concentration is 0.05% w/v±0.025%.

[0017] In some embodiments, the one or more thermal stablilizers comprise sucrose and arginine. In some embodiments, the sucrose concentration is 5%±1% (w/v) and the Arginine concentration is 70 mM±14 mM .